Curr Treat Options Neurol (2015) 17: 21
DOI 10.1007/s11940-015-0348-3

Critical Care Neurology (K Sheth, Section Editor)

Management of Pediatric Traumatic Brain Injury

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Published online: 9 April 2015

This article is part of the Topical Collection on *Critical Care Neurology*

Keywords Pediatric neurocritical care · Traumatic brain injury · Children · Intracranial pressure · Pediatric head injury

Opinion statement

Pediatric severe traumatic brain injury continues to be a major cause of disability and death. Rapid initial airway and hemodynamic stabilization is critical, followed by the need for immediate recognition of intracranial pathology that requires neurosurgical intervention. Intracranial hypertension and cerebral hypoperfusion have been recognized as major insults after trauma and management should be directed at preventing both. Sedation with opioids, moderate hyperventilation to arterial carbon dioxide level of 35–40 mmHg, hyperosmolar therapy with 3 % saline or mannitol, normothermia, and cerebrospinal fluid drainage continue to be the cornerstones of initial management of intracranial hypertension (intracranial pressure >20 mmHg). Refractory intracranial hypertension is treated with high-dose barbiturate therapy to achieve medical burst suppression on electroencephalography and decompressive craniectomy. In addition, those children require antiepileptic medications for seizure prophylaxis, adequate nutritional management, and early physical therapy and rehabilitation referrals. Most of the evidence for care of children with brain injury comes from center-specific practice and experience rather than objective data. This lack of evidence provides the ground for ongoing research; nevertheless, outcomes after traumatic brain injury continue to show improvement.

Introduction

Traumatic brain injury (TBI) is the leading cause of death in children between 1 and 19 years of age in the most recent data from the CDC [1]. In the USA, TBI in children is responsible for 60,000

hospitalizations and approximately 7400 deaths [2]. It is estimated that 125,000 children are living with a TBI-related disability, with overall life costs for those individuals estimated at $60.4 billion [2]. The care of children admitted with brain injury requires a multidisciplinary team including emergency physicians, pediatric critical care, trauma care, neurosurgery, neurology, physical therapy and rehabilitation medicine, a nutritionist, and social work services. Recent evidence suggests that the presence of multidisciplinary team assessments and protocol-driven approach to this vulnerable patient population could improve outcomes [3•]. For the past 40 years, TBI has been classified predominantly by the level of consciousness after the injury occurs. This assessment—almost exclusively defined by the Glasgow Coma Scale (GCS) score—has been trichotomized to define severe (GCS ≤8), moderate (GCS 9–12), and mild (GCS ≥13) injuries. Because of the high mortality and morbidity associated with TBI, most of the recent advances in management have focused on children within the severe TBI cohort. For that reason, this review will focus on this segment of the disease spectrum.

Outcomes of TBI are affected by the extent of primary brain injury and the severity and duration of secondary insults [3•], and contemporary pediatric neurotrauma care focuses on mitigating or avoiding such secondary injuries. A synthesis of the current state of the literature and evidenced-based recommendations on management strategies has been published—the "Guidelines for the Acute Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents" published first in 2003 and then updated in 2012 [4, 5••]. Other recent advances in the publication and dissemination of information regarding the management of children with TBI include the sponsoring and publication of papers regarding "common data elements" [6–9]. These manuscripts outline the data elements that all future TBI studies must collect—so that studies may be adequately compared and even combined to glean as much information as possible from the data.

The initial management of TBI begins with stabilization in the field and emergency department—including the rapid assessment for primary injuries, a secondary survey to assess for all life-threatening problems, and early neuroimaging to identify intracranial pathology requiring surgical intervention [5••, 10, 11]. Endotracheal intubation for children with severe TBI, GCS <9, is recommended, along with admission to a pediatric intensive care unit (PICU) with cardiorespiratory and hemodynamic monitoring. Avoidance of hypoxemia, hypercarbia, hypotension, hyperthermia, and high intracranial pressure (ICP) and maintenance of age-appropriate cerebral perfusion pressure (CPP) are the overall goals of PICU care. Intracranial pressure monitoring can be accomplished via different modalities, but the most commonly used are intraparenchymal catheters and external ventricular drainage (EVD) devices. The EVD has an added advantage of cerebrospinal fluid (CSF) drainage. In addition, some intraparenchymal transducers are coupled with the ability of brain tissue oxygenation monitoring (PbO_2), although no randomized controlled pediatric studies are available to determine treatment thresholds. Figaji and colleagues demonstrated in a prospective study that brain tissue oxygenation is poorly predicted by clinical and physiological factors commonly measured in the pediatric ICU. In addition, reduced PbO_2 levels are associated with poor outcomes [12, 13].

While the absolute goals for optimal ICP have never been demonstrated for either adults or children with severe TBI, most data supports that an ICP <20 mmHg is a reasonable goal for both populations [14–17]. On the other hand, CPP thresholds for children are generally believed to be age specific. Chambers and colleagues have reported critical CPP thresholds to be 48 mmHg for age 2–6 years, 54 mmHg for 7–10 years, and 58 mmHg for 11–16 years [18]. In a more recent prospective, observational study by Allen and colleagues, a target CPP above 50 mmHg in 6–17-year olds and above 40 mmHg in 0–5-year-old age group was associated with improved outcomes [19••]. The pediatric literature has not directly addressed the question of whether ICP control or CPP maintenance or the combination of both is the critical factor in affecting outcome. In a retrospective study by Stippler and colleagues [20], CPP rather than ICP or PbO_2 was the one physiologic variable that correlated with outcome after pediatric TBI. Mehta and colleagues demonstrated that in children <2 years of age, those with unfavorable outcome had more hourly readings of CPP <45 mmHg compared to the favorable outcome group. There was no difference between the number of hourly readings of ICP >20 mmHg between

the two groups [21]. In our practice, we treat ICP spikes >20 mmHg aggressively while maintaining CPP targets.

In the following section, we will summarize the care of the child with severe TBI with a specific focus on management of intracranial hypertension.

Treatment

After stabilization outlined above, there are pharmacological, interventional, and surgical procedures to relieve intracranial pressure.

Pharmacologic treatment

Sedatives and analgesics

Sedatives and analgesics are required for general care of all critically ill children to achieve a level of anesthesia for invasive procedures, to synchronize respiratory efforts with the ventilator and to provide pain/anxiety relief due to their illness. General classes of sedatives/analgesics used in children with TBI include opioids, benzodiazepines, barbiturates, propofol, ketamine, and etomidate. A recent systematic review in adults with TBI concluded that there is no strong evidence for the use of any sedative agent over another [22]. No pediatric studies have attempted to compare different sedatives. Most centers use a combination of opioids and benzodiazepines for pain control and sedation in children with severe TBI. Ketamine is rarely used due to reports of inducing increased ICP, propofol is avoided due to propofol infusion syndrome, and etomidate continues to be used as an induction agent to facilitate airway management, but its use in the PICU is rare due to its adrenal suppressive effects.

Opioids

Opioids are used primarily as analgesic agents in children with TBI, while some of the various agents within this class have some sedative effect at the higher end of their therapeutic range. As a practical matter, opioids can be administered as single doses or as continuous infusions, with fentanyl and morphine being most commonly used in children. Fentanyl is more lipophilic than morphine and has the advantage of faster onset of action, but both can accumulate with long-term use and could hinder the neurologic exam. Administration of opioids during intracranial hypertension crises is very common, with the goal of determining whether the episode is related to the sedation level of the child. Despite their common use, the pediatric literature lacks evidence to support the use of these agents. In adults with TBI, the reports have been contradictory. In four reports, three report an increase in ICP and the fourth reports a decrease in mean arterial pressure after administration of fentanyl or morphine [23–26]. It has been suggested that the observed increase in ICP may be related to cerebral autoregulatory reflexes that maintain CPP. However, in a retrospective review in adults, fentanyl reduced ICP by 3.77–8.22 mmHg [27].

Standard dosage	Fentanyl 1–3 mcg/kg bolus, 1–2 mcg/kg/h infusion (starting dose). Morphine 0.05–0.1 mg/kg/dose, 20–30 mcg/kg/h infusion (starting dose).
Contraindications	Allergy.
Main drug interactions	Central nervous system depressants.
Main side effects	Sedation, apnea, hemodynamic effects. Morphine can cause histamine release.
Special points	Fentanyl should be injected slowly to avoid rigid chest. Morphine requires dose adjustments in patients with renal impairment.
Cost/cost-effectiveness	Fentanyl 50 mcg syringe=1 USD. Morphine 50 mg vial=0.55 USD.

Benzodiazepines

Benzodiazepines are GABA receptor agonists, thereby decreasing activity within the brain by activating this inhibitory pathway. Midazolam has a more rapid onset in comparison to lorazepam and diazepam, but midazolam has an active metabolite and accumulates with prolonged infusions. Benzodiazepines, in general, reduce cerebral metabolic rate of oxygen, ICP, and cerebral blood flow and increase seizure threshold. However, adverse effects of benzodiazepines on cardiac performance (thereby affecting mean arterial pressure (MAP) and CPP) have been observed [28]. While studies in children are lacking, those from adult TBI victims found that midazolam and propofol were equally efficacious in ICP control with no noted adverse event [29–31].

Standard dosage	Midazolam 0.05–0.2 mg/kg bolus, infusion 0.05–0.1 mg/kg/h (starting dose).
Contraindications	Hypersensitivity.
Main drug interactions	Central nervous system depressants.
Main side effects	Sedation, apnea, hemodynamic effects, emergence delirium.
Special points	Dose adjustments in patients with liver insufficiency.
Cost/cost-effectiveness	Midazolam 5 mg/ml vial=3.9 USD.

Barbiturates

Like benzodiazepines, barbiturates are GABA agonists that have a long history of use in TBI. Thiopentone (sodium thiopental) has been historically used for rapid induction in TBI patients due to its high lipid solubility, but it has been discontinued in North America. Pentobarbital continues to be available and used for the control of refractory intracranial hypertension after other medical therapies have failed [5••]. When used for this indication, a common goal to achieve is electroencephalograph (EEG) evidence of burst suppression. Barbiturates lower ICP by reduction of cerebral metabolic rate and alteration of vascular tone. Due to direct myocardial and central vasomotor depressant effects, hypotension should be anticipated and treated aggressively. A Cochrane review by Roberts and colleagues suggested that barbiturates should not be used prophylactically to prevent ICP elevations nor as a maintenance sedative agent [32•]. In a report by Pittman and colleagues, pentobarbital was effective in reducing ICP >30 mmHg in 52 % of children, but mortality rate was still substantial in those patients despite reduction in ICP [33]. In a more recent retrospective review by Mellion and colleagues, refractory intracranial hypertension was controlled within 6 h of addition of pentobarbital in 30 % of patients [34].

Standard dosage	Pentobarbital 5 mg/kg bolus then 1–2 mg/kg/h infusion.
Contraindications	Hypersensitivity.
Main drug interactions	Central nervous system depressants.
Main side effects	Sedation, apnea, laryngospasm, hemodynamic effects, hepatotoxicity.
Special points	Could result in severe bradycardia and hypotension.
Cost/cost-effectiveness	Pentobarbital 50 mg/ml vial=20.65 USD.

Propofol

	Propofol is a widely used sedative in adults because its rapid onset of action and short half-life makes it the ideal drug to allow for frequent neurologic assessments. However, its use as a long-term (meaning several days) sedative in children has been limited due to reports of propofol infusion syndrome associated with long-term infusions. One pediatric report demonstrated a reduction in ICP and maintenance of CPP with the combination of propofol with dopamine [35]. In an adult study in 1990, propofol resulted in a significant reduction in ICP (from 1.5 to 7.3 mmHg) and CPP [27, 36]. In a randomized controlled trial by Kelly and colleagues where propofol was compared to morphine sulfate, they found improved ICP control and decreased need for additional interventions in those patients [37]. As mentioned previously, propofol was comparable with midazolam in patients with head injury [29, 30]. Despite its potential benefit in children with TBI, propofol use is not recommended due to "black box" warnings from the US FDA.
Standard dosage	Propofol 1–2 mg/kg bolus; infusion not recommended.
Contraindications	Hypersensitivity to propofol, egg products, or soy products.
Main drug interactions	Central nervous system depressants.
Main side effects	Hemodynamic instability, apnea, hypertriglyceridemia, propofol infusion syndrome.
Special points	Could result in severe hypotension.
Cost/cost-effectiveness	Propofol 10 mg/ml vial=0.93 USD.

Etomidate

	Etomidate is a GABA receptor agonist that is predominantly used as an induction agent for endotracheal intubation or general anesthesia [38]. In 1979, Moss and colleagues demonstrated the efficacy of etomidate in causing a significant ICP reduction with a minimal reduction in MAP and CPP [39]. Similarly, in pediatrics, Bramwell and colleagues demonstrated that a single dose of etomidate is effective at reducing ICP while maintaining MAP and CPP [40]. However, the use of etomidate is currently being reviewed in TBI patients because of its potent effects on the adrenal axis—leading to relative adrenal insufficiency in animals and in some clinical reports.
Standard dosage	Etomidate 0.2 mg/kg bolus.
Contraindications	Hypersensitivity.
Main drug interactions	No known significant interactions.
Main side effects	Hypertension, laryngospasm, adrenal suppression.

Special points	High doses of etomidate have been associated with EEG epileptiform spikes in patients with seizure disorder, EEG slowing, and isoelectricity.
Cost/cost-effectiveness	Etomidate 2 mg/ml vial=1.18 USD.

Ketamine

Ketamine is an *N*-methyl-D-aspartate receptor antagonist that has been historically unused in TBI due to reports of intracranial hypertension in patients with altered CSF flow dynamics [41–43]. In a more recent randomized study, ketamine-midazolam and sufentanil-midazolam were compared as target controlled infusions and ketamine was found to have no significant change on ICP or CPP [44]. In children, Bar-Joseph and colleagues performed a prospective study where ketamine was administered to control refractory intracranial hypertension. Ketamine reduced ICP by 33 % while maintaining CPP [45]. However, the study was not included in the current guidelines because the severity of TBI was not reported for the subjects.

Standard dosage	Ketamine 1–2 mg/kg bolus.
Contraindications	Hypersensitivity, conditions in which increased blood pressure could be dangerous.
Main drug interactions	Central nervous system depressants.
Main side effects	Laryngospasm, emergence reactions.
Special points	Maintains hemodynamic stability in catecholamine nondepleted states.
Cost/cost-effectiveness	Ketamine 10 mg/ml vial=0.99 USD.

Neuromuscular blockade

Neuromuscular blockade (NMB) is utilized in children with severe TBI to improve compliance with mechanical ventilation, reduce metabolic demand, and eliminate shivering. No systematic studies in either children or adults have investigated the utility of NMB in TBI. Chin and colleagues [46••] performed a secondary analysis of the "Cool Kids" trial [47••], and they found that children requiring NMB had a higher number of daily ICP >20 mmHg, longer PICU, and hospital length of stay but no difference in outcome or complications to those who did not require NMB. A potential explanation is the increased severity of illness or injury in the group requiring NMB. A retrospective review of adult patients receiving early NMB showed no improvement in outcomes, but no data was presented about ICP [48]. A recent systematic review by Sanfilippo and colleagues confirmed the lack of strong evidence for the effect of NMB on ICP and outcomes [49•]. Of note, if continuous NMB is used as part of routine care of patient with TBI, continuous EEG is needed to assess for posttraumatic seizures [50].

Hyperosmolar therapy

Osmotic agents are used to reduce brain tissue edema. In cases of intracranial hypertension, they are used after or concurrently with sedation, mild hyperventilation, and CSF drainage to achieve ICP control. The following is a description of the use of both mannitol and hypertonic saline.

Mannitol

Mannitol has been the traditional agent to use for raised ICP after its introduction in the 1960s. A 20 % mannitol dose of 1 g/kg was thought to

	reduce ICP by two mechanisms: first, an immediate reduction in blood viscosity leading to reflex vasoconstriction, reduction of cerebral blood volume, and reduction in ICP [51]. However, Diringer and colleagues challenged this theory in a study of six adult TBI patients where they found an increase in cerebral blood volume [52•]. The second mechanism is related to an osmotic effect leading to movement of water from brain parenchyma to the systemic circulation, and this would require an intact blood-brain barrier [53]. In a recent Cochrane review [54••], mannitol was found to be associated with decreased mortality when compared to pentobarbital [55] but increased mortality when compared to hypertonic saline [56].
Standard dosage	Mannitol 20 % 0.25–1 g/kg bolus.
Contraindications	Hemodynamic instability, renal insufficiency.
Main drug interactions	Aminoglycosides, antihypertensive agents.
Main side effects	Hypotension, gastrointestinal discomfort, fever.
Special points	To minimize adverse renal effects, adjust dose to keep serum osmolality <320 mOsm/L.
Cost/cost-effectiveness	Mannitol powder=0.05 USD.

Hypertonic saline

	The movement of sodium across the blood-brain barrier is low; therefore, the movement of water from the brain into the systemic circulation is mostly affected by the osmolality to which sodium is the major contributor. Various formulations are available, ranging from 2 to 23.4 % saline concentrations. In adult literature, a dose of hypertonic saline resulted in a reduction of ICP by 3.04–9.76 mmHg [27], and given as bolus therapy, it was more effective than mannitol in lowering the cumulative and daily ICP burdens after severe TBI [57••]. In a pediatric double-blind, crossover study, 3 % saline resulted in a more significant reduction in ICP than 0.9 % saline [58]; similarly, in a randomized controlled trial, 1.7 % saline was superior to lactated Ringer's solution in ICP reduction and the number of interventions needed to reduce ICP [59].
Standard dosage	3 % saline 3–10 ml/kg bolus, titrate infusion to effect.
Contraindications	Severe hypernatremia.
Main drug interactions	Lithium.
Main side effects	Central pontine myelinosis (due to rapid correction of hyponatremia), hyperchloremic metabolic acidosis.
Special points	Could be used up to a serum osmolality of 360 mOsm/L.
Cost/cost-effectiveness	Low cost.

Anticonvulsant therapy

Infants and children have lower seizure thresholds [5••], and seizures after traumatic brain injury could lead to secondary brain damage. Nonconvulsive seizures are often unrecognized and can be detected in up to 50 % of patients when continuous EEG is aggressively utilized. In a prospective pediatric cohort after TBI, 42.5 % of patients had seizures and 16 % of those were subclinical [60•]. Therefore, the use of continuous EEG monitoring could be very beneficial

for children. Administration of anticonvulsants after TBI is generally intended to prevent posttraumatic seizures and not to prevent the development of epilepsy—which has a complex pathophysiology that is poorly understood. In children with severe TBI, Lewis and colleagues found that phenytoin administration resulted in significantly less seizures compared to those not receiving the medication using a nonrandomized study design [61]. In a randomized, double-blind pediatric study, Young and colleagues found similar seizure rates between both phenytoin and placebo groups for the first 48 h of admission. Pediatric guidelines continue to recommend considering antiseizure prophylaxis for children with severe TBI [5••].

Standard dosage	Phenytoin 20 mg/kg bolus then 2.5 mg/kg Q12h (titrate for therapeutic levels).
Contraindications	Hypersensitivity, sinus bradycardia, heart block.
Main drug interactions	Drugs metabolized by CYP3A4.
Main side effects	Bradycardia, hypotension with rapid IV push, agranulocytosis, seizures.
Special points	Slow IV injection should be used to avoid cardiovascular collapse.
Cost/cost-effectiveness	Fosphenytoin 500 mg phenytoin equivalent/10 ml=0.61 USD.

Corticosteroids

The pediatric guidelines recommend against the use of corticosteroids for ICP control or outcome [5••]. This recommendation was based on two pediatric randomized controlled trials by Fanconi and Kloti that demonstrated that steroids had no effect on ICP, CPP, or outcome and patients treated with steroids have an increased incidence of infections [62, 63].

Interventional procedures

Cerebrospinal fluid drainage

The role of CSF drainage is to reduce the volume of the contents of the intracranial vault in an effort to lower ICP. The placement of an external ventricular drain for ICP measurements provides this additional benefit. Pediatric guidelines support the use of CSF drainage as a method to control ICP [5••].

Hyperventilation

Hyperventilation reduces ICP by lowering cerebral blood flow (and thereby cerebral blood volume) by cerebral vasoconstriction of arterioles. Concerns have escalated that this maneuver can lead to subclinical cerebral ischemia [64]. In addition, hyperventilation leads to a reduction in cerebral oxygenation and additional ischemia [65]. Despite, the 2003 pediatric guidelines recommendation to use moderate hyperventilation for the treatment of intracranial hypertension, Curry and colleagues found a similar incidence of severe hypocarbia (arterial carbon dioxide <30 mmHg) pre- and postguidelines. In addition, they found a mortality adjusted odds ratio of 4.18 in the cases with two episodes of severe hypocarbia [66]. The 2012 guidelines continue to recommend avoiding

severe hyperventilation in the first 48 h after injury; our current practice is targeting an arterial carbon dioxide level of 35–40 mmHg.

Temperature control

Hyperthermia after acute TBI has a role in increased metabolic demands, lipid peroxidation, inflammation, excitotoxicity, and lowering seizure thresholds and, hence, increasing secondary brain injury. Three pediatric trials have explored the effect of 24–72 h of moderate therapeutic hypothermia (32–33 °C) compared to normothermia on ICP and neurologic outcome after TBI [15, 47••, 67]. Moderate hypothermia was effective in controlling ICP but had no effect on neurologic outcome at 3 and 6 months after injury, and in the study by Hutchison and colleagues, it was associated with a worse neurologic outcome, although those patients had severe hypocapnia as part of their treatment protocol.

Surgery

Decompressive craniectomy

The pediatric literature on decompressive craniectomy has been in the form of prospective or retrospective case series with only one randomized controlled trial by Taylor and colleagues [68], which was not included in the pediatric guidelines due to the inclusion of patients with GCS of 9. Each of those studies has used a different type and timing for the procedure, which makes it difficult to draw conclusions, but all procedures were effective at ICP reduction in cases of refractory intracranial hypertension [68–70]. The study by Taylor and colleagues demonstrated improved neurologic outcome in patients treated with decompressive craniectomy within 6 h of randomization in comparison to standard therapy [68].

Other treatments

Nutritional management

Nutritional support is essential for children with severe TBI. It provides the energy needed for tissue repair, wound healing, and optimal organ function. One pediatric study has met the pediatric guidelines inclusion criteria by Briassoulis and colleagues [71], who found no advantage in feeding patients an immune-enhancing diet. There has been no other randomized trials that address the optimal amount of energy needed and what route is preferred.

Glucose control

Hyperglycemia has been reported to be associated with worse neurologic outcome in children, but no clear cutoff has been determined for which treatment should be started [72–74].

Patient positioning

It is generally recommended to maintain patient head position at 30°, with a stable cervical spine collar. Both of those will allow adequate venous drainage and prevent increases in ICP.

Emerging therapies

- Stem cell therapy in traumatic brain injury (two trials completed, results pending)
- Lactate therapy after traumatic brain injury (currently enrolling)
- Intravenous progesterone in patients with severe TBI (completed study, results pending)

Compliance with Ethics Guidelines

Conflict of Interest
Haifa Mtaweh declares no conflict of interest.
Michael J. Bell declares the receipt of grants from the (US) National Institutes of Health.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the authors.

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